

Pathophysiological and pharmacological implications of elucidating the molecular bases of the interaction between HBV and the bile acid transporter NTCP

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Binding of hepatitis B virus to its cellular receptor alters the expression profile of genes of bile acid metabolism. Oehler N, Volz T, Bhadra OD, Kah J, Allweiss L, Giersch K, Bierwolf J, Riecken K, Pollok JM, Lohse AW, Fehse B, Petersen J, Urban S, Lüttgenheftmann M, Heeren J, Dandri M. *Hepatology* 2014; 60(5): 1483-93.

Comment:

In the paper by Oehler, *et al.*, the authors have investigated whether the interaction between HBV and the major carrier accounting for bile acid uptake by hepatocytes from sinusoidal blood, the Na^+ -taurocholate cotransporting polypeptide (NTCP), results in alterations in bile acid homeostasis and subsequently in an impairment in the hepatic metabolism of cholesterol and other lipids. To carry out this study, the authors have used HBV-infected and uninfected human liver chimeric mice. Moreover, to validate the findings obtained in mice the authors have used liver biopsy samples collected from individuals chronically infected with HBV. The most dramatic change observed affected the expression of the rate-limiting enzyme converting cholesterol into bile acids, i.e., CYP7A1, which was markedly (12-fold) up-regulated upon HBV infection in mice. Similar observation was obtained when liver biopsies from HBV-infected patients were investigated. The identification of NTCP as the plasma membrane tag

recognized by HBV and, therefore, as the specific receptor accounting for viral entry in hepatocytes,¹ constituted an important landmark in the field of viral hepatitis because this finding explained an important question that had remained unanswered for long time, i.e., why HBV selectively infects hepatocytes. The facts that NTCP, the major bile acid uptake transporter in hepatocytes² is located at the basolateral membrane of differentiated cells, and that hepatocyte polarization, in addition to the differentiation status, plays a key role in the infection process,³ matched with the organ-selectivity of HBV infection. However, the molecular link was still missing. By elucidating the molecular bases of the interaction of the virus with the transporter, the paper by Oehler, *et al.* constitutes an important step forward in this field, contributing to understand the pathophysiological and pharmacological consequences of this interaction. On one hand the fact that HBV-NTCP interaction reduces bile acid uptake, which would be reflected by increased serum levels of these steroids, could be used as an early biomarker of the infection because the raise in serum bile acids would occur before hepatocellular damage and hence cholestasis develop. At this respect, previous studies have suggested the existence of a certain interaction between bile acid homeostasis and HCV infection.⁴ Those studies indicated that the measurement of serum levels of bile acids in combination with those of ferritin could give important information regarding the absence of a sustained response to antiviral therapy in patients with chronic HCV.⁴ However, in contrast to HBV, the molecular bases for the relationship between HCV and bile acid homeostasis has not yet been established. According to the paper by Oehler, *et al.*, the HBV-induced alteration in lipid metabolism is not limited to bile acid homeostasis, since other aspects involved in the response to lower intracellular levels of bile acids, such as compensatory cholesterol provision, are also affected. In addi-

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tion, other viral components, such as the HBV X protein (HBx), can also affect lipid metabolism by inducing activation of lipogenic genes and fatty acid accumulation in the liver, which, in turn, could favour the pathogenesis of hepatitis by promoting steatosis, oxidative stress, and eventually liver inflammation.^{5,6}

From the pharmacological point of view, the elucidation of the actual mechanism of HBV-induced impairment in NTCP function may permit to establish the bases of novel pharmacological strategies to overcome some problems associated to HBV infection. Thus, the authors have treated uninfected chimeric mice with Myrcludex-B, a myristoylated lipopeptide derived from the pre-S1 domain of the HBV envelope. Since this component of the viral particle plays a crucial role in HBV infectivity,⁷ this drug is able to inhibit viral entry in hepatocytes. Owing to this characteristic, Myrcludex-B is currently under clinical evaluation. The results of the elegant experiments using Myrcludex-B were similar to the actual infection with complete HBV viral particles. The authors concluded that HBV-induced up-regulation of CYP7A1 was due, in a first step, to the interaction of NTCP with the pre-S1 domain of the viral protein. As a consequence, a complex panel of metabolic alterations was triggered. Importantly, the changes did not include impairment in the expression of either NTCP or the canalicular pump BSEP, the two major transporters required for bile salt homeostasis.⁸ This permits to speculate with the possibility of using pre-S1 domain inhibitors to pharmacologically manipulate NTCP function and hence bile acid/cholesterol metabolism. However, the potential existence of drug-drug interactions must not be disregarded. Inversely, although there are several studies supporting a role of HBV infection in biliary disease, it would be interesting to elucidate whether situations accompanied by decreased expression/function of NTCP, either when it occurs secondarily due to cholestasis-induced intracellular accumula-

tion of bile acids⁹ or primarily due to genetic variations in *SLC10A1* gene with clinical¹⁰ or subclinical¹¹ consequences, are characterized by a reduced susceptibility to HBV infection.

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